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CASE REPORT

Thalamic lesion and epilepsy with generalized seizures, ESES and spike-wave paroxysms—Report of three cases

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Summary We report three patients, who have thalamic lesion and secondary generalized epilepsy with generalized spike wave pattern. The first two patients have unilateral perinatal lesion, one with generalized tonic—clonic seizures on awakening the other with Landau—Kleffner-like syndrome. During the course of the disease both children developed electrical status epilepticus in slow wave sleep (ESES). The third patient has a dominantly unilateral thalamic tumor and epilepsy that mimics juvenile myoclonic epilepsy. All the patients have a lesion located in the inferior-medial-posterior part of the thalamus.

The role of some thalamic and subthalamic nuclei in the generalized spike-wave electrical pattern patophysiology is discussed, with emphasis on the possible role of the inhibitory system from the zona incerta.

Introduction

Generalized spike-wave (GSW) discharges are considered to be a hallmark of idiopathic generalized epilepsy (IGE). The involvement of the thalamus in the pathophysiology of GSW discharges is well-known. The reticular thalamic nucleus is regarded to be the pacemaker structure for the rhythmic cortical oscillations in spindle frequency range, which are assumed to transform into GSW activity in IGE.[1,2] The thalamus is also involved in secondary epileptogenesis. Recently the nucleus anterior thalami and the zona incerta were also proved to have an important role in bilateral SW synchrony.[3—5]

We report three patients, in whom dominantly unilateral thalamic lesion, although different in type, lead to features that mimic electro-clinical features of generalized epilepsy with spike wave pattern and in two cases ESES.

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Case 1

A 9-year-old girl was born at term, with 9/10 Apgar score, but the amniotic fluid was spoiled with meconium. Her father had febrile convulsions. Early psychomotor development was normal. When she was 4-years-old, she started having generalized tonic–clonic seizures on awakening with more pronounced jerking on the left part of the body and version of the head to left, three to four times per year. Her EEG showed bilateral, synchronous, frontal predominant, 2.5 Hz GSW and generalized polyspike-wave (GPSW) pattern. At the age of 8 she had a 2.5 Hz SW non-convulsive status epilepticus, with psychomotor slowing and confusion. She responded to valproate and lamotrigine bitherapy. She came to our institute in a seizure-free state because of cognitive deterioration. Sleep EEG was performed the first time then, showing electrical status epilepticus in slow wave sleep (ESES), and bifrontal, or right frontal spikes in awake state and REM sleep. Brain MRI showed tissue loss (presumed perinatal injury) in the medial-posterior-inferior part of the right thalamus and mild right hippocampal sclerosis (Fig. 1). The ESES pattern responded only to very high doses of steroids.

Case 2

The 10-year-old male patient's perinatal history was unremarkable. At the age of 6 weeks he developed subarachnoidal bleeding due to Vitamin K deficiency. His psychomotor development was slightly slowed. When he was 2-years-old, he developed epilepsy with nocturnal motor brachiofacial seizures and GTCSs. At the age of 4 the seizure type changed to atonic seizures and atypical absences with generalized 2.5 Hz GSW discharges on awake EEG and ESES during sleep. His cognitive abilities declined, he developed word-finding problems, but his understanding remained fairly good. He was diagnosed as atypical Landau–Kleffner syndrome. The brain MRI revealed right thalamic infarction located in the postero-medial-inferior part of the thalamus and moderately enlarged lateral ventricles (Fig. 2). The ESES pattern was resistant to benzodiazepines, valproate, lamotrigine and ACTH.

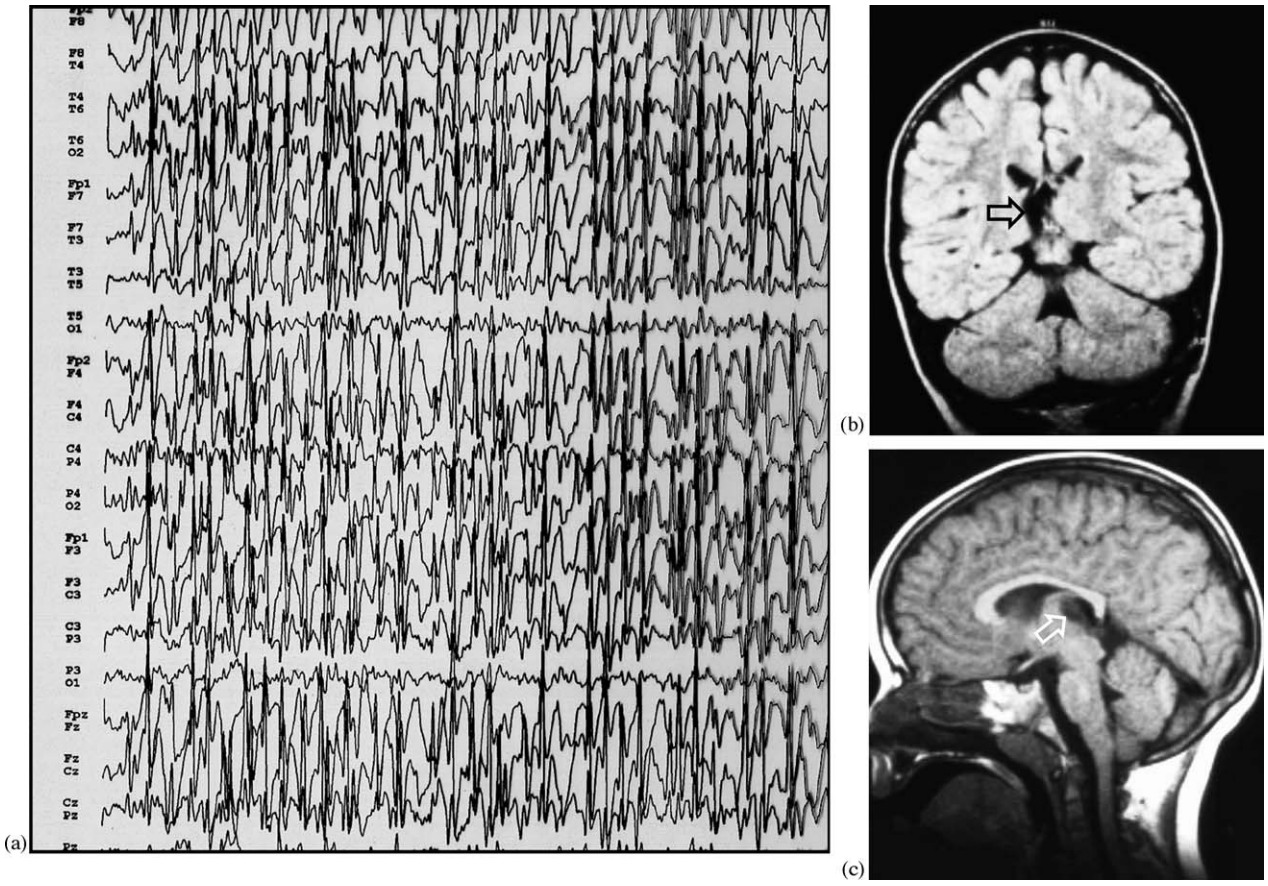

Figure 1 Patient 1: (a) EEG: ESES; (b) coronal FLAIR MRI; (c) sagital T1 weighted MRI: perinatal lesion in the right thalamus (arrows) in the posterior-medial-inferior region.

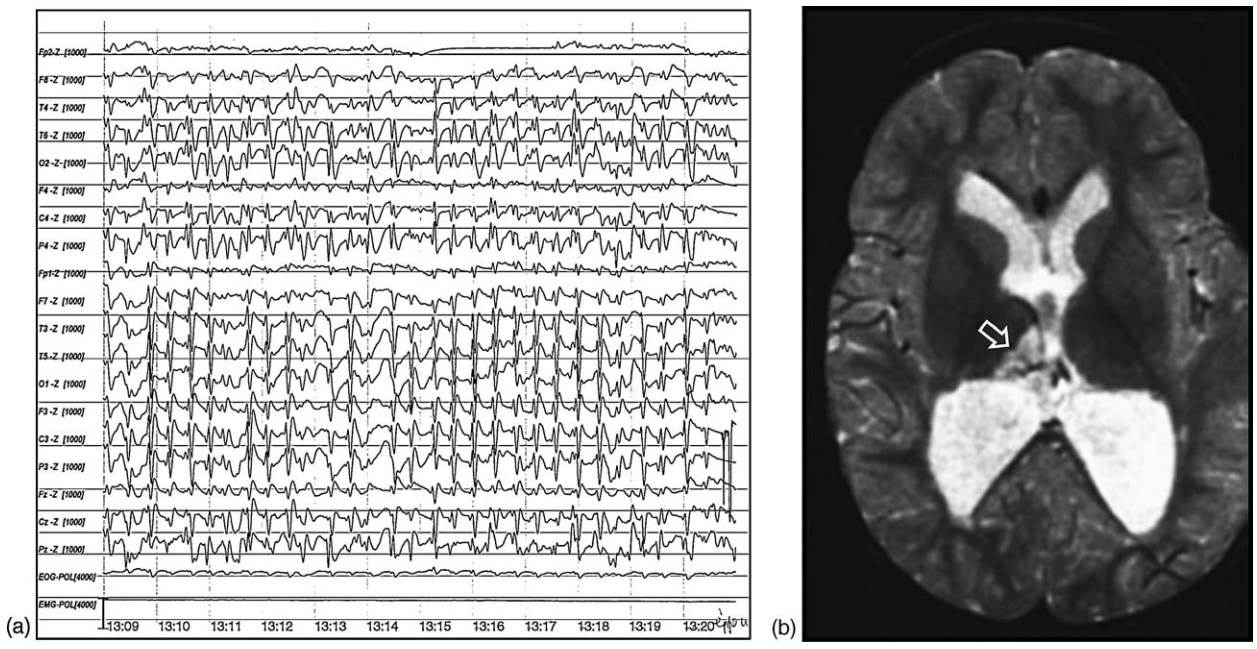

Figure 2 Patient 2: (a) EEG: ESES; (b) axial T2 weighted MRI: perinatal lesion in the right thalamus (arrow), mild hydrocephalus.

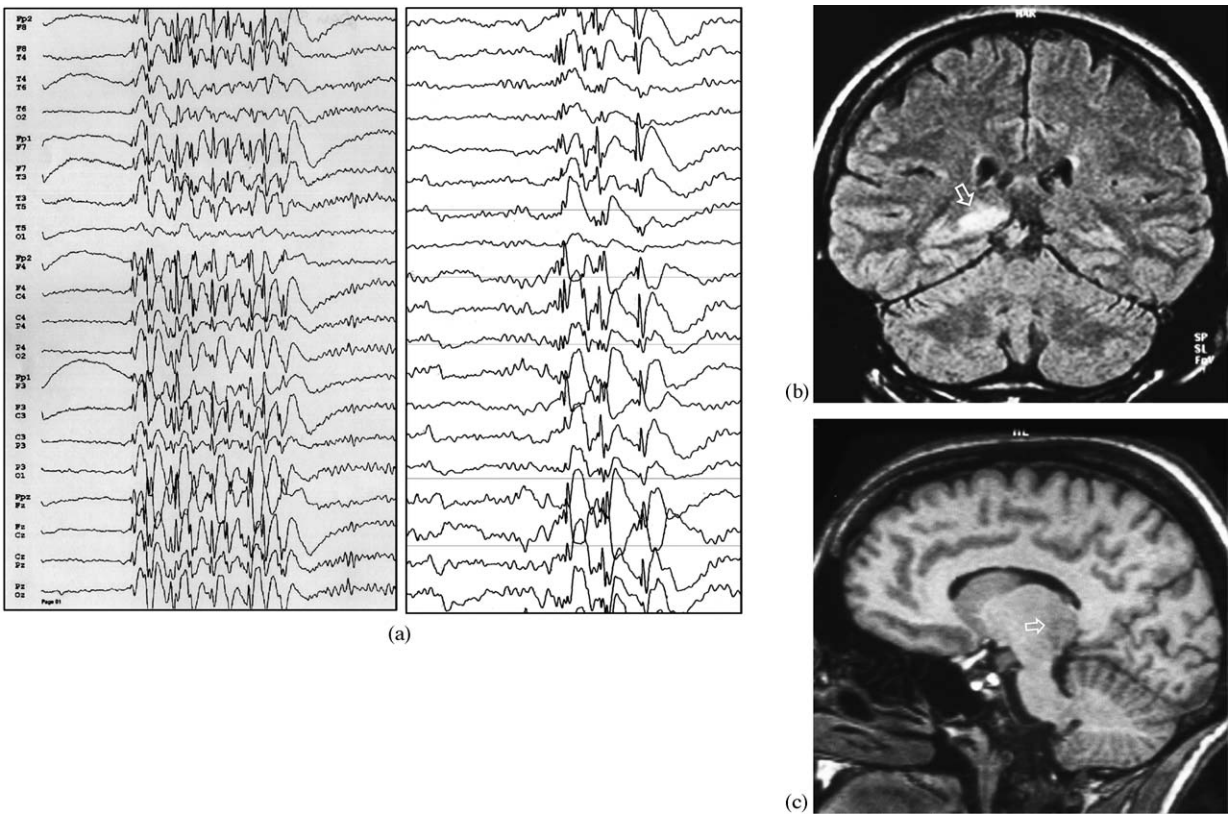

Figure 3 Patient 3: (a) EEG: generalized PSW pattern; (b) coronal FLAIR MRI; (c) sagital T1 weighted MRI: tumor involving the infero-mediodorsal part of the right thalamus (arrows).

Case 3

The 32-year-old female patient was born from an uneventful pregnancy and delivery; her psychomotor development was normal. She has no neurological abnormality and has normal IQ. Her epilepsy began at the age of 14, with generalized tonic–clonic seizures on awakening. No EEG abnormality was found at that time. We saw her first at the age of 27, when a long-term EEG was performed, showing 3 Hz GSW and GPSW discharges in sleep. The diagnosis of idiopathic generalized epilepsy was made. We lost her for follow-up for the next 3 years. After another GTCS on awakening she came to us again. Meanwhile she had absence-like seizures too. Brain MRI performed because of pharmaco-resistancy showed a space occupying lesion, without contrast enhancement involving the right postero-infero-medial part of the thalamus extending slightly to the contralateral side of the thalamus and to the mesencephalon (Fig. 3). Repeated MRI investigations did not show progression, the lesion was considered a low-grade tumor (astrocytoma probably). Currently under valproate-phenytoin-levetiracetam tri-therapy she has been seizure-free for 30 months, but the EEG did not changed.

Discussion

It has been recognized for a long time that bilateral central midline structure lesions (or compression) can result in GSW discharges with or without seizures. It was described in cases of shunted hydrocephalus and in hypothalamic lesions.[6,7] So far, only few reports of unilateral thalamic lesion and epilepsy were published, but most of them showed bilateral synchronous GSW discharges. Inghilleri reported a child with ischemic lesion involving the left thalamus, who developed absence status with bilateral GSW discharges.[8] Monteireo,[9] Incorpora,[10] our group[11] and recently Guzetta[12] reported children with epilepsy with continuous spike-waves during slow wave sleep after perinatal thalamic injury. The last author showed that ESES is not rare in this patient population. Contrary to the mentioned cases our third patient is a young adult with a destructive lesion, a tumor in the infero-medial thalamus, in whom the GSW and seizure pattern behaves exactly the same way as the GSW pattern in JME concerning morphology and vigilance-dependency.

In the generation of GSW the cortex is considered to be the decisive factor, while the thalamus is involved secondarily. The primary role in the synchronized activity of the thalamus and cortex is attributed to the reticular nucleus.[1,2] Rat experiments showed corticothalamic coherence not only in the reticular nucleus, but in the nucleus anterior thalami (NAT) as well providing electrophysiological evidence for the role of the anterior thalamus in the propagation of seizure activity between subcortex and cortex.[13] In rats stimulation of the anterior nuclei of the thalamus exerted anti-seizure effect.[14–16] One of the possible anticonvulsive mechanisms of vagus nerve stimulation is via the thalamus.[17]

However, contrary to cases published by Guzetta, who had lesions of the reticular nucleus and anterior part of the thalamus, all our patients have a unilateral (patient 1, 2) or predominantly unilateral (patient 3) lesion of the inferior medial, more dorsal part of the thalamus, leaving the shell-shaped reticular nucleus on the surface of the thalamus and the anterior part intact. The lesions of our patients involve the region of the dorsal intralaminar nuclei, the nucleus dorsomedialis thalami and the floor of the thalamus, and in case 2 and 3, the subthalamic region as well. However, from 12 patients of Gusetta et al. who exhibited ESES, the dorsomedial thalamic region was involved also in 7, compared to those without ESES (20 patients), in whom this posterior medial type of lesion was present only in 5, according to their Table 2.[12] Therefore, the contradiction between the two studies is not so conspicuous, and possibly their theoretical frame in which they emphasize the role of the anterior and lateral part of the thalamus is not established enough. Recently, the role of the subthalamically located zona incerta was documented which has a GABA-ergic inhibitory effect on the higher order thalamic nuclei projecting to the neocortex, suggesting that selective GABA-ergic control of relay cell activity will result in effective, state-dependent gating of thalamocortical information.[4,18] The lesion of this system can lead to disinhibition and marked activation of the paroxysmal activity in sleep.

In our cases similarly to other published reports the lesions were unilateral, but the SW activity is bilateral. A secondary bilateral synchrony with propagation through the corpus callosum is possible.

The patient reported by Inghilleri had an ischemic lesion involving the left thalamus after a top-of-the-basilar syndrome and absence status with bilateral spike-and-wave discharges.[8] In top of the basilar syndrome, the subthalamic region and the paramedian thalamic structures were damaged too.

Although ESES has been originally described in patients without evidence of brain lesion, it has been increasingly recognized in various focal cortical lesional epilepsies. Published cases with early thalamic injury had lesions more widespread than

our patients. Incorpora's case 2 is the most similar to our patient 1 (in both, the localization and extent of the lesion, as well as in some details of the clinical picture).[10]

Another theoretical possibility, although highly unlikely one is, that lesions were only activating an otherwise silent genetically determined GSW pattern.

The coexisting ipsilateral HS in the first patient needs a comment. Similarly to Monteiro's case, our patient's hippocampus was also atrophic, but with sclerosis. It would be attractive to assume a common etiology for both the thalamic and hippocampal damage, as they share common vascular supply, but it is unlikely because the nature of these two alterations is different. As the midline thalamic region is a part of the thalamolimbic circuits, other type of functional connectivity is more likely.[19]

Conclusions

Our cases provide new arguments supporting that early thalamic lesion can predispose to childhood epilepsy with ESES, probably in addition to cortical pathology and genetic predisposition. Children with thalamic injury should be monitored closely for paroxysmal activity during sleep and cognitive deterioration. Lesions of the inferior-medial-posterior thalamic structures might have a role in the pathogenesis of bilateral SW discharges and ESES by mechanism of disinhibition, possibly through the GABA-ergic system of zona incerta and its projections.

Our third patient is the first reported adult case with acquired focal thalamic lesion and SW discharges.

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